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=> fil reg
FILE 'REGISTRY' ENTERED AT 16:53:39 ON 09 DEC 2003
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STRUCTURE FILE UPDATES:    8 DEC 2003  HIGHEST RN 625077-42-1
DICTIONARY FILE UPDATES:   8 DEC 2003  HIGHEST RN 625077-42-1

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http://www.cas.org/ONLINE/DBSS/registryss.html

=> d ide can tot l1

L1   ANSWER 1 OF 3  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   113189-02-9  REGISTRY
CN   Blood-coagulation factor VIII, procoagulant (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   AHF-A
CN   Antihemophilic factor
CN   Antihemophilic factor A
CN   Antihemophilic globulin
CN   Bioclate
CN   Blood-coagulation factor VIII
CN   Blood-coagulation factor VIIIc
CN   Coagulation factor VIIIc
CN   Factor VIII
CN   Koate DVI
CN   Monoclate
CN   Monoclate-P
MF   Unspecified
CI   MAN
SR   CA
LC   STN Files:   ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, CA, CAPLUS,
       CBNB, CEN, CIN, DIOGENES, DRUGNL, DRUGPAT, DRUGUPDATES, IPA, MSDS-OHS,
       PHAR, PIRA, PROMT, TOXCENTER, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
            1700 REFERENCES IN FILE CA (1907 TO DATE)
              43 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
            1702 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE   1:  139:362806

REFERENCE   2:  139:362805

REFERENCE   3:  139:362778

REFERENCE   4:  139:359345

REFERENCE   5:  139:345630
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REFERENCE 6: 139:337302

REFERENCE 7: 139:337300

REFERENCE 8: 139:336912

REFERENCE 9: 139:336550

REFERENCE 10: 139:336229

L1 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2003 ACS on STN
RN 109319-16-6 REGISTRY
CN Blood-coagulation factor VIII, von Willebrand's (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Antigens, blood-coagulation factor VIII-related
CN Blood platelet-aggregating factor
CN Blood-coagulation factor VIII
CN Blood-coagulation factor VIII antigen
CN Blood-coagulation factor VIII-related antigen
CN Blood-coagulation factor VIIIR
CN **Factor VIII**
CN Ristocetin cofactor
CN Ristocetin-von Willebrand factor
CN von Willebrand's factor
MF Unspecified
CI MAN
SR CA
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CEN, CIN, DIOGENES, EMBASE, IPA, PIRA, PROMT, TOXCENTER, USPAT2, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
3650 REFERENCES IN FILE CA (1907 TO DATE)
74 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3659 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:364163

REFERENCE 2: 139:363446

REFERENCE 3: 139:362781

REFERENCE 4: 139:362151

REFERENCE 5: 139:362134

REFERENCE 6: 139:361116

REFERENCE 7: 139:359540

REFERENCE 8: 139:349510

REFERENCE 9: 139:349298

REFERENCE 10: 139:349229

L1 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2003 ACS on STN
RN 9001-27-8 REGISTRY
CN Blood-coagulation factor VIII, complex (9CI) (CA INDEX NAME)
OTHER NAMES:
CN AHF
CN AHF-HP

CN AHG
CN Amofil
CN Beriate HS
CN Biostate P
CN Blood-coagulation factor VIII
CN **Factor VIII**
CN Factorate
CN Fanhdi
CN FVIII-THP/SD
CN Haemate HS
CN Haemate P
CN Haemoctin SDH
CN Hemate P
CN Hemofil
CN Hemofil M
CN Humafac
CN Humate P
CN Koate HP
CN Nordiocto
CN Octonativ-M7
CN Profilate
CN Thromboplastinogen
DR 9035-62-5, 114046-09-2
MF Unspecified
CI COM, MAN
LC STN Files: AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CBNB, CEN, CHEMLIST, CIN, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, PHAR, PHARMASEARCH, PIRA, PROMT, RTECS*, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
3589 REFERENCES IN FILE CA (1907 TO DATE)
66 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3590 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:358433

REFERENCE 2: 139:357967

REFERENCE 3: 139:349043

REFERENCE 4: 139:347728

REFERENCE 5: 139:345632

REFERENCE 6: 139:345182

REFERENCE 7: 139:345181

REFERENCE 8: 139:341652

REFERENCE 9: 139:333055

REFERENCE 10: 139:318625

=> d his

(FILE 'HOME' ENTERED AT 15:27:10 ON 09 DEC 2003)
SET COST OFF

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     FILE 'REGISTRY' ENTERED AT 15:32:38 ON 09 DEC 2003
                E FACTOR VIII/CN
L1              3 S E3

     FILE 'HCAPLUS' ENTERED AT 15:33:16 ON 09 DEC 2003
L2           8289 S L1
L3           3570 S BLOOD()(COAGULAT? OR CLOT?)()FACTOR VIII
L4           4986 S VON WILLEBRAND? FACTOR
L5           3884 S (COAGULAT? OR CLOT?)()FACTOR VIII
L6           6989 S FACTOR VIII
L7           4171 S (COAGULAT? OR CLOT?)()FACTOR VIII#
L8           3750 S BLOOD()(COAGULAT? OR CLOT?)()FACTOR VIII#
L9           5107 S VON()(WILLEBRAND? OR WILLEBRAND S)()FACTOR
L10           331 S BLOOD? FACTOR VIII#
L11            38 S THROMBOPLASTINOGEN?
L12         11515 S L2-L11
                E VOORBERG J/AU
L13            44 S E3-E6
                E VANDENBRINK/AU
                E VANDEN BRINK/AU
                E VAN DENBRINK/AU
                E VAN DEN BRINK/AU
L14            10 S E20,E21
                E DEN BRINK/AU
                E DENBRINK/AU
                E BRINK/AU
                E TURENHOUT E/AU
L15            10 S E4,E5
                E STICHTING/PA,CS
                E SANQUI/PA,CS
L16           100 S E5,E6
L17            24 S E7-E28
L18            45 S L12 AND L13-L17
                SEL DN AN 21
L19             1 S E1-E3 AND L18
L20          2603 S L12 AND ANTIBOD?
L21          1676 S L20 AND (?PROTEIN? OR ?PEPTIDE? OR AMINOACID? OR AMINO ACID?)
L22             3 S L20 AND (PROTEIN? OR PEPTIDE? OR AMINO ACID?)/SC,SX
                E PROTEIN/CT
                E PROTEIN/CW
L23           579 S L20 AND E3,E7
                E PROTEINS/CT
                E PROTEIN SEQUENCE/CT
                E E11+ALL
L24           156 S L20 AND E2+NT
                E E9+ALL
L25           102 S L20 AND E4+NT
                E PEPTIDE/CW
L26           138 S L20 AND E3,E4
                E POLYPEPTIDE/CW
L27             5 S L20 AND E3,E5
                E PEPTIDE/CT
L28           246 S L20 AND E88+NT
                E E88+ALL
                E POLYPEPTIDE/CT
                E E10+ALL
L29             0 S L20 AND E1
L30           417 S L20 AND E2,E3
L31          1700 S L21-L30
                E AMINO ACID/CT
L32           124 S L20 AND E42+NT
L33          1709 S L31,L32
```

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L34         239 S L33 AND ?IMMUNOGLOBULIN?
                E IMMUNOGLOBULIN/CT
                E E4+ALL
L35         513 S E2
L36         339 S E4
L37        5501 S E14
                E IMMUNOGLOBULINS/CT
L38       29558 S E43
L39        1074 S E72
L40          81 S E73
L41         314 S E74
L42        1833 S E81
L43       12764 S E83
L44        1694 S E36
L45         138 S L33 AND L35-L44
L46         239 S L34,L45
L47         153 S L33 AND (IGA OR IGD OR IGG OR IGM OR IGG4)
L48         110 S L33 AND (IMMUNOGLOBULIN OR IG)()(A OR D OR G OR M OR G4)
L49          25 S L33 AND (IMMUNOGLOBULIN OR IG)(L)(HEAVY OR LIGHT)(L)CHAIN
L50          45 S L33 AND (IMMUNOGLOBULIN OR IG)(L)FRAGMENT
L51         306 S L46-L50
L52          12 S L33 AND ?SCFV?
L53           1 S L33 AND (IMMUNOGLOBULIN OR IG)(L)SINGLE(L)CHAIN
L54         193 S L33 AND FV?
L55           0 S L33 AND (?SCFVEL? OR ?SCFVIT?)
L56           0 S L33 AND (?FVEL? OR ?FVIT?)
L57           0 S L54 AND (EL14 OR 1T2 OR IT2)
L58          10 S L33 AND VARIABLE REGION
L59         459 S L51-L58
L60           2 S L33 AND (DP10 OR DP14 OR DP15 OR DP31 OR DP47 OR DP49 OR DP77
L61         459 S L59,L60
L62          49 S L33 AND (IMMUNOGLOBULIN OR IG)(L)(A1 OR A3 OR C1 OR C2 OR M O
L63         459 S L61,L62
L64           6 S L33 AND CDR3
L65           0 S L33 AND CDR 3
L66           0 S L33 AND CD R3
L67           0 S L33 AND CD R 3
L68         459 S L63,L64
L69         480 S L33 AND (A1 OR M OR B OR A3 OR C1 OR C2)
L70         752 S L68,L69
L71          12 S L18 AND L70
L72           3 S L19,L71 AND (PD<=19980508 OR PRD<=19980508 OR AD<=19980508)
L73         427 S L70 AND (PD<=19980508 OR PRD<=19980508 OR AD<=19980508)
                E HEMOPHIL/CT
L74        1076 S E5
                E E4+ALL
L75        2792 S E5
                E E7+ALL
L76         860 S E5
L77          40 S E5/BI OR E6/BI OR E7/BI
L78        3682 S E8/BI
L79       13425 S HEMOPHILI? OR HAEMOPHIL?
L80         100 S L73 AND L74-L79
L81          55 S L80 AND  (HEMOPHILI? OR HAEMOPHIL?)()A
L82          45 S L80 NOT L81
                SEL DN AN 1 2 8 11 19 42
L83           6 S L82 AND E1-E18
                SEL DN AN 1 2 4 5 12 17 22 48 50 L81
L84           9 S L81 AND E19-E45
L85          17 S L72,L83,L84 AND L2-L84
L86          16 S L85 AND (IG OR IGA IR IGD OR IGG OR IGM OR IGG4 OR A1 OR A2 O
L87          13 S L85 AND (?SCFV? OR SC OR FV? OR IMMUNOGLOBULIN? OR CD43)
L88          17 S L85-L87
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L89            8 S L12 AND CDR3
L90            0 S L12 AND CDR 3
L91            0 S L12 AND CD R 3
L92            0 S L12 AND CD R3
L93           15 S L12 AND COMPLEMENT?(L)DETERMIN?(L)REGION
L94            0 S L12 AND COMPLEMENT?(L)DETERMIN?(L)R3
L95           20 S L89,L93
L96           14 S L95 AND (PD<=19980508 OR PRD<=19980508 OR AD<=19980508)
L97            3 S L12 AND CDR
L98            3 S L97 AND (PD<=19980508 OR PRD<=19980508 OR AD<=19980508)
L99           14 S L96,L98
                  SEL DN AN 2 7 8
L100           3 S L99 AND E46-E54
L101          19 S L88,L100 AND L2-L100

     FILE 'REGISTRY' ENTERED AT 16:53:39 ON 09 DEC 2003

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 16:53:46 ON 09 DEC 2003
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FILE COVERS 1907 - 9 Dec 2003  VOL 139 ISS 24
FILE LAST UPDATED: 8 Dec 2003  (20031208/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> d all tot l101

L101 ANSWER 1 OF 19  HCAPLUS  COPYRIGHT 2003 ACS on STN
AN   2002:429466  HCAPLUS
DN   137:19402
ED   Entered STN:  07 Jun 2002
TI   Antigenic polypeptide sequences of Factor VIII
     , and fragments and/or epitopes of these sequences for use in treatment
     and diagnosis of hemophilia
IN   Laub, Ruth; Di Giambattista, Mario
PA   Belg.
SO   U.S. Pat. Appl. Publ., 25 pp., Cont.-in-part of U. S. Ser. No. 765,837.
     CODEN: USXXCO
DT   Patent
LA   English
IC   ICM  C07K005-00
     ICS  C07K007-00; C07K016-00; C07K017-00; A61K038-00; A61K038-04;
          C07K001-00; C07K014-00; A61K035-14; G01N033-53; C12P021-08
NCL  435007100
CC   15-8 (Immunochemistry)
     Section cross-reference(s): 14
FAN.CNT 2
```

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002068303	A1	20020606	US 2001-853080	20010509 <--
	BE 1008491	A3	19960507	BE 1994-666	19940714 <--
	WO 9602572	A2	19960201	WO 1995-BE68	19950714 <--
	WO 9602572	A3	19970213		
	W: CA, JP, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 2003147900	A1	20030807	US 1999-765837	19990907 <--
	WO 2002090542	A2	20021114	WO 2002-BE70	20020506
	W: CA, JP				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
PRAI	BE 1994-666	A	19940714 <--		
	WO 1995-BE68	W	19950714 <--		
	US 1999-765837	A2	19990907		
	US 2001-853080	A	20010509		

AB The present invention is related to the antigenic **polypeptide** sequence of **Factor VIII**. The antigenic epitopes of **Factor VIII** are used in treatment and diagnosis of **hemophilia**. Inhibitors of **Factor VIII** (i.e. **antibodies**) can be removed from patient serum using the antigenic epitopes bound to a chromatog. column and the serum can be reinjected to the patient.

ST **hemophilia** therapy diagnosis **factor VIII** epitope **antibody**

IT **Hemophilia**
(**A**; epitopes of **factor VIII** for treatment and diagnosis of **hemophilia**)

IT **Immunoglobulins**
RL: ADV (Adverse effect, including toxicity); DGN (Diagnostic use); REM (Removal or disposal); BIOL (Biological study); PROC (Process); USES (Uses)
(G2; epitopes of **factor VIII** for treatment and diagnosis of **hemophilia**)

IT **Immunoglobulins**
RL: ADV (Adverse effect, including toxicity); DGN (Diagnostic use); REM (Removal or disposal); BIOL (Biological study); PROC (Process); USES (Uses)
(**G4**; epitopes of **factor VIII** for treatment and diagnosis of **hemophilia**)

IT **Immunoglobulins**
RL: ADV (Adverse effect, including toxicity); DGN (Diagnostic use); REM (Removal or disposal); BIOL (Biological study); PROC (Process); USES (Uses)
(**G**; epitopes of **factor VIII** for treatment and diagnosis of **hemophilia**)

IT **Antibodies**
RL: DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anti-idiotypic; epitopes of **factor VIII** for treatment and diagnosis of **hemophilia**)

IT Affinity
B cell (lymphocyte)
Blood serum
Coagulation
Epitopes
Filters
Hemophilia
Human
Immunotherapy
Liquid chromatographic columns
T cell (lymphocyte)

Test kits
(epitopes of **factor VIII** for treatment and diagnosis of **hemophilia**)

IT **Antibodies**
RL: ADV (Adverse effect, including toxicity); DGN (Diagnostic use); REM (Removal or disposal); BIOL (Biological study); PROC (Process); USES (Uses)
(epitopes of **factor VIII** for treatment and diagnosis of **hemophilia**)

IT BCR (**B** cell receptors)
Phospholipids, biological studies
TCR (T cell receptors)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(epitopes of **factor VIII** for treatment and diagnosis of **hemophilia**)

IT **Peptides, biological studies**
RL: DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(epitopes of **factor VIII** for treatment and diagnosis of **hemophilia**)

IT Circulation
(extracorporeal; epitopes of **factor VIII** for treatment and diagnosis of **hemophilia**)

IT **Immunoglobulins**
RL: ADV (Adverse effect, including toxicity); DGN (Diagnostic use); REM (Removal or disposal); BIOL (Biological study); PROC (Process); USES (Uses)
(**fragments**; epitopes of **factor VIII** for treatment and diagnosis of **hemophilia**)

IT Diagnosis
(serodiagnosis; epitopes of **factor VIII** for treatment and diagnosis of **hemophilia**)

IT 9001-29-0, Factor X 9013-55-2, Blood-coagulation factor XI
109319-16-6
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(epitopes of **factor VIII** for treatment and diagnosis of **hemophilia**)

IT **9001-27-8, Factor VIII** 177359-62-5
177359-63-6 177359-64-7 177359-65-8 177359-66-9 177359-67-0
177359-69-2 177359-70-5 177359-71-6 177359-73-8 177359-74-9
177359-75-0 177359-76-1 177359-77-2 433929-54-5 433929-55-6
433929-56-7 433929-57-8 433929-58-9 433929-59-0 433929-60-3
433929-61-4 433929-62-5 433929-63-6 433929-64-7 433929-65-8
433929-66-9 433929-67-0 433929-68-1 433929-69-2 433929-70-5
433929-71-6 433929-72-7
RL: DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(epitopes of **factor VIII** for treatment and diagnosis of **hemophilia**)

L101 ANSWER 2 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **2001:73453** HCAPLUS
DN **134:130398**
ED Entered STN: 01 Feb 2001
TI Modified **factor VIII**
IN Lollar, John S.
PA Emory University, USA
SO U.S., 86 pp., Cont.-in-part of U.S. 5,859,204.
CODEN: USXXAM
DT Patent
LA English
IC ICM C12P021-04
ICS C12P021-06; A61K035-14; C07K014-00

NCL 435069600
CC 16-6 (Fermentation and Bioindustrial Chemistry)
Section cross-reference(s): 3
FAN.CNT 12

	PATENT NO.	KIND	DATE		APPLICATION NO.	DATE	
PI	US 6180371	B1	20010130		US 1998-37601	19980310	<--
	CA 2258502	AA	19971231		CA 1997-2258502	19970626	<--
	CA 2258502	C	20030429				
	CA 2322508	AA	19990916		CA 1999-2322508	19990310	<--
	WO 9946274	A1	19990916		WO 1999-US5193	19990310	<--
	W: AU, CA, CN, CZ, HU, IL, JP, KR, MX, NO, NZ, PL, RU						
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE						
	AU 9929956	A1	19990927		AU 1999-29956	19990310	<--
	AU 747644	B2	20020516				
	EP 1062224	A1	20001227		EP 1999-911272	19990310	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI						
	JP 2002506076	T2	20020226		JP 2000-535651	19990310	<--
	NZ 506771	A	20021126		NZ 1999-506771	19990310	<--
	US 6458563	B1	20021001		US 2000-523656	20000310	<--
	NO 2000004497	A	20001107		NO 2000-4497	20000908	<--
	US 2003166536	A1	20030904		US 2002-131510	20020423	<--
	US 2003068785	A1	20030410		US 2002-187319	20020628	<--
PRAI	US 1996-670707	A2	19960626	<--			
	US 1992-864004	A2	19920407	<--			
	US 1994-212133	A2	19940311	<--			
	WO 1994-US13200	A2	19941115	<--			
	WO 1997-US11155	A2	19970626	<--			
	US 1998-37601	A	19980310	<--			
	WO 1999-US5193	W	19990310				
	US 1999-315179	A3	19990520				
	US 2000-523656	A3	20000310				

AB Specific **amino acid** loci of human **factor VIII** interact with inhibitory **antibodies** of **hemophilia** patients who have developed such **antibodies** after being treated with **factor VIII**. Modified **factor VIII** is disclosed in which the **amino acid** sequence is changed by a substitution at one or more of the specific loci. The modified **factor VIII** is not inhibited by inhibitory **antibodies** against the **A2** or **C2** domain epitopes. The modified **factor VIII** is useful for **hemophiliacs**, either to avoid or prevent the action of inhibitory **antibodies**.

ST **factor VIII** human porcine hybrid immunogenicity decrease

IT Animal tissue culture
(mammalian; modified **factor VIII** with decreased immunogenicity)

IT Immunity
(modified **factor VIII** with decreased immunogenicity)

IT 244065-54-1 244065-55-2 309307-00-4, **Blood-coagulation factor VIII** (human)
RL: PRP (Properties)
(**amino acid** sequence; modified **factor VIII** with decreased immunogenicity)

IT **113189-02-9P, Factor VIII**
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(modified **factor VIII** with decreased

immunogenicity)
IT 201874-76-2 243905-33-1
RL: PRP (Properties)
(nucleotide sequence; modified **factor VIII** with decreased immunogenicity)
IT 140742-96-7 148391-60-0 153065-62-4 217895-20-0, 6: PN: WO0174903 SEQID: 6 unclaimed DNA 217895-23-3, 8: PN: WO0168109 SEQID: 8 unclaimed DNA 243905-15-9, 7: PN: WO0168109 SEQID: 7 unclaimed DNA 243905-16-0, 9: PN: WO0168109 SEQID: 9 unclaimed DNA 243905-17-1 243905-18-2 243905-19-3 243905-20-6 243905-21-7 243905-22-8 243905-23-9 243905-24-0 243905-25-1 243905-26-2 243905-27-3 243905-28-4 243905-29-5 243905-30-8 243905-31-9 243905-32-0 250353-64-1 309308-34-7, 1: PN: WO0071141 SEQID: 7 unclaimed DNA 309308-35-8, 2: PN: WO0071141 SEQID: 8 unclaimed DNA 309308-36-9, 3: PN: WO0071141 SEQID: 9 unclaimed DNA 309308-37-0, 4: PN: WO0071141 SEQID: 10 unclaimed DNA 309308-38-1, 5: PN: WO0071141 SEQID: 11 unclaimed DNA 309308-39-2, 6: PN: WO0071141 SEQID: 12 unclaimed DNA
RL: PRP (Properties)
(unclaimed nucleotide sequence; modified **factor VIII**)
IT 150791-63-2, **Blood-coagulation factor VIII** (mouse precursor reduced) 308390-66-1
RL: PRP (Properties)
(unclaimed **protein** sequence; modified **factor VIII**)
IT 309262-12-2
RL: PRP (Properties)
(unclaimed sequence; modified **factor VIII**)
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Anon; EP 0306968 A2 1988 HCAPLUS
(2) Anon; WO 9107438 1990 HCAPLUS
(3) Anon; WO 9411503 1994 HCAPLUS
(4) Anon; WO 9703191 1997 HCAPLUS
(5) Anon; WO 9703193 1997 HCAPLUS
(6) Church; Proc Natl Acad Sci USA 1984, V81, P6934 HCAPLUS
(7) Dominguez, O; Nucleic Acids Res 1994, V22, P3247 HCAPLUS
(8) Eaton, D; Biochemistry 1986, V25(26), P8343 HCAPLUS
(9) Fulcher, C; Proc Natl Acad Sci USA 1985, V82, P7728 HCAPLUS
(10) Gitcher, J; Nature 1984, V312, P326
(11) Healy, J; Blood 1996, V88, P4209
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(13) Lollar; US 5663060 1997 HCAPLUS
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L101 ANSWER 3 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **2000:841997** HCAPLUS
DN **134:14739**

ED Entered STN: 01 Dec 2000
TI **Blood-coagulation factor VIII** variants and hybrids with decreased immunoreactivity and having procoagulant activity
IN Lollar, John S.
PA Emory University, USA
SO PCT Int. Appl., 172 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K035-14
ICS C07H021-04; C12P021-04; C12P021-06
CC 7-5 (Enzymes)
Section cross-reference(s): 3, 15, 63
FAN.CNT 12

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 2000071141	A1	20001130	WO 2000-US13541	20000516	
	W: AU, CA, JP					
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
	US 6376463	B1	20020423	US 1999-315179	19990520	<--
	EP 1200105	A1	20020502	EP 2000-932530	20000516	
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY					
	JP 2003508019	T2	20030304	JP 2000-619444	20000516	
	AU 765442	B2	20030918	AU 2000-50237	20000516	
PRAI	US 1999-315179	A	19990520			
	US 1992-864004	A2	19920407	<--		
	US 1994-212133	A2	19940311	<--		
	WO 1994-US13200	A2	19941115	<--		
	US 1996-670707	A2	19960626	<--		
	WO 2000-US13541	W	20000516			

AB Specific **amino acid** loci of human **blood-coagulation factor VIII** interact with inhibitory **antibodies** of **hemophilia** patients who have developed such **antibodies** after being treated with **factor VIII**. Modified **factor VIII** is disclosed in which the **amino acid** sequence is changed by a substitution at one or more **amino acids** of positions 484-508 of the **A2** domain. The **A2** domain epitope was identified by construction of human-porcine and human-mouse hybrid **factor VIII** mols. and by site-specific alanine-scanning mutagenesis of the **A2** domain. The modified **factor VIII** variants are useful as clotting factor supplements for **hemophiliacs**.
ST **coagulation factor VIII** hybrid variant immunoreactivity procoagulant; sequence **coagulation factor VIII** hybrid variant; epitope mapping **coagulation factor VIII A2** domain
IT **Antibodies**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(autoantibodies, immunoreactivity toward; **blood-coagulation factor VIII** variants and hybrids with decreased immunoreactivity and having procoagulant activity)
IT Coagulants
Mouse
Mutagenesis
Protein engineering
Swine
(**blood-coagulation factor VIII**

variants and hybrids with decreased immunoreactivity and having procoagulant activity)

IT cDNA sequences
(for **blood-coagulation factor VIII** variants and hybrids with decreased immunoreactivity and having procoagulant activity)

IT Epitopes
(mapping; **blood-coagulation factor VIII** variants and hybrids with decreased immunoreactivity and having procoagulant activity)

IT **Protein sequences**
(of **blood-coagulation factor VIII** variants and hybrids with decreased immunoreactivity and having procoagulant activity)

IT **Hemophilia**
(treatment of; **blood-coagulation factor VIII** variants and hybrids with decreased immunoreactivity and having procoagulant activity)

IT 150791-63-2, **Blood-coagulation factor VIII** (mouse precursor reduced) 153065-59-9, 20-2351-**Blood-coagulation factor VIII** (human precursor reduced) 244065-54-1, **Blood-coagulation factor VIII**, procoagulant (swine precursor) 244065-55-2, **Blood-coagulation factor VIII**, procoagulant [de-(**B** domain)] (swine precursor) 308390-66-1
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(**amino acid** sequence; **blood-coagulation factor VIII** variants and hybrids with decreased immunoreactivity and having procoagulant activity)

IT **113189-02-9D, Blood-coagulation factor VIII**, site-specific and hybrid variants
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(**blood-coagulation factor VIII** variants and hybrids with decreased immunoreactivity and having procoagulant activity)

IT 140742-96-7, DNA (human **blood-coagulation factor VIII** cDNA plus flanks) 148391-60-0, DNA (mouse **blood-coagulation factor VIII** cDNA plus flanks) 153065-62-4, DNA (swine **blood-coagulation factor VIII** fragment-specifying cDNA) 201874-76-2, DNA (swine **blood-coagulation factor VIII** cDNA plus flanks) 243905-33-1, DNA (swine procoagulant **blood-coagulation factor VIII** [de-(**B** domain)] precursor-specifying cDNA plus flanks)
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(nucleotide sequence; **blood-coagulation factor VIII** variants and hybrids with decreased immunoreactivity and having procoagulant activity)

IT 217895-20-0, 6: PN: WO0174903 SEQID: 6 unclaimed DNA 217895-23-3, 8: PN: WO0168109 SEQID: 8 unclaimed DNA 243905-15-9, 7: PN: WO0168109 SEQID: 7 unclaimed DNA 243905-16-0, 9: PN: WO0168109 SEQID: 9 unclaimed DNA 243905-17-1 243905-18-2 243905-19-3 243905-20-6 243905-21-7 243905-22-8 243905-23-9 243905-24-0 243905-25-1 243905-27-3 243905-28-4 243905-29-5 243905-30-8 243905-31-9 243905-32-0 250353-64-1 309308-34-7, 1: PN: WO0071141 SEQID: 7 unclaimed DNA 309308-35-8, 2: PN: WO0071141 SEQID: 8 unclaimed DNA 309308-36-9, 3: PN:

WO0071141 SEQID: 9 unclaimed DNA 309308-37-0, 4: PN: WO0071141 SEQID: 10 unclaimed DNA 309308-38-1, 5: PN: WO0071141 SEQID: 11 unclaimed DNA 309308-39-2, 6: PN: WO0071141 SEQID: 12 unclaimed DNA
RL: PRP (Properties)
(unclaimed nucleotide sequence; **blood-coagulation factor VIII** variants and hybrids with decreased immunoreactivity and having procoagulant activity)

IT 243905-26-2 309262-12-2
RL: PRP (Properties)
(unclaimed sequence; **blood-coagulation factor VIII** variants and hybrids with decreased immunoreactivity and having procoagulant activity)

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Amano; Blood 1998, V91(2), P538 HCAPLUS
(2) Fulcher; Proc Natl Acad Sci 1985, V82, P7728 HCAPLUS
(3) Lollar; J Biol Chem 1992, V267(33), P23652 HCAPLUS
(4) Scandella; Proc Natl Acad Sci 1988, V85, P6152 HCAPLUS

L101 ANSWER 4 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **1999:736932** HCAPLUS
DN **131:350266**
ED Entered STN: 19 Nov 1999
TI Method for diagnosis and treatment of **haemophilia-A** patients with **factor VIII** inhibitors
IN **Voorberg, Johannes Jacobus; Van Den Brink, Edward Norbert; Turenhout, Ellen Anne Maria**
PA Stichting **Sanquin** Bloedvoorziening, Neth.
SO PCT Int. Appl., 61 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N015-13
ICS C07K016-36; C07K016-42; A61K039-395; A61K038-37; C12Q001-68; A61K039-395; A61K038-37
CC 15-3 (Immunochemistry)
Section cross-reference(s): 1, 3, 14
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9958680	A2	19991118	WO 1999-NL285	19990507	<--
	WO 9958680	A3	20010222			
	W: AU, CA, JP, US					
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
	CA 2327587	AA	19991118	CA 1999-2327587	19990507	<--
	AU 9938538	A1	19991129	AU 1999-38538	19990507	<--
	AU 760678	B2	20030522			
	EP 1095143	A2	20010502	EP 1999-921292	19990507	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
	JP 2002514422	T2	20020521	JP 2000-548471	19990507	<--
PRAI	EP 1998-201543	A	19980508	<--		
	WO 1999-NL285	W	19990507			

AB Anti-**factor VIII antibodies** (**factor VIII** inhibitors) present in the plasma of patients with acquired **hemophilia** were characterized by immunopptn. and neutralization expts. The **antibodies** directed against the **factor VIII** light chain consisted exclusively of **IgG4**. CDNAs coding for human **factor VIII** inhibitor are disclosed. **IgG4** specific probes and primers for detection of **factor VIII** inhibitors and for producing recombinant **polypeptides** are provided. An **antibody** directed against a human

factor VIII inhibitor is provided. Pharmaceutical compns. which contain recombinant **IgG4 Fv** fragment and **blood-coagulation factor VIII** also provided.

ST human **factor VIII** inhibitor **IgG4** cDNA sequence; diagnosis therapy **hemophilia A** **factor VIII** inhibitor **IgG4**

IT **Hemophilia**
(**A**; method for diagnosis and treatment of **hemophilia -A** patients with **factor VIII** inhibitors)

IT **Protein motifs**
(**CDR3** of **IgG4**; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT **Immunoglobulins**
RL: ADV (Adverse effect, including toxicity); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**G4, factor VIII** inhibitors, gene for, and recombinants, **Fv fragment** of; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT Test kits
(**IgG4** labeled primers and probes containing; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT Primers (nucleic acid)
Probes (nucleic acid)
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific, labeled; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT **Antibodies**
RL: ARU (Analytical role, unclassified); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(against **IgG4** (**factor VIII** inhibitor); method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT cDNA sequences
(for **factor VIII** inhibitors (**IgG4**) of human; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT Oligonucleotides
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(labeled, with radioactive atom or group, enzyme, fluorescent or luminescent group, dye or biotin; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT Blood analysis
Gene therapy
Genetic engineering
Molecular cloning
(method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT Diagnosis
(mol.; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT **Protein sequences**
(of **factor VIII** inhibitors (**IgG4**) of human; method for diagnosis and treatment of **hemophilia-**

A patients with **factor VIII** inhibitors)

IT Epitopes
(of **factor VIII** inhibitors, specificity of; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT Hemostatics
(pharmaceutical composition containing recombinant **IgG4 Fv** fragment and **factor VIII**; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT PCR (polymerase chain reaction)
(quant.; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT **9001-27-8, Factor VIII**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**IgG4** as inhibitors of, pharmaceutical composition containing recombinant **IgG4 Fv** fragment and; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT 250281-75-5
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, conIgG1-4; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT 250281-76-6
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huIgG4; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT 226984-00-5
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huJH3forSal; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT 226984-08-3
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huJH4-5forSal; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT 226984-12-9
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huJH6forSal; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT 226983-94-4
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huJH1-2forSal; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT 250353-40-3
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huVH1backNco; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT 165888-40-4

RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huVH2aback; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT 250353-46-9
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huVH2backNco; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT 165888-41-5
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huVH3aback; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT 250353-48-1
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huVH3backNco; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT 250281-77-7
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huVH4aback; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT 250281-86-8
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huVH4backNco; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT 250281-78-8
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huVH5aback; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT 250281-87-9
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huVH5backNco; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT 167731-78-4, PN: US5962255 SEQID: 61 unclaimed DNA
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huVH6aback; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT 250281-88-0
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huVH6backNco; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT 165888-39-1
RL: ARG (Analytical reagent use); PRP (Properties); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**IgG4** specific primer, huVHlaback; method for diagnosis and

treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT 250207-98-8P 250207-99-9P 250281-89-1P 250282-00-9P 250282-09-8P 250282-10-1P 250282-11-2P 250282-12-3P 250282-13-4P 250282-14-5P 250282-15-6P 250282-18-9P 250282-22-5P
RL: ADV (Adverse effect, including toxicity); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**amino acid** sequence; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

IT 225914-21-6 225914-22-7 250285-51-9 250285-52-0 250285-53-1 250285-54-2
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(nucleotide sequence; method for diagnosis and treatment of **hemophilia-A** patients with **factor VIII** inhibitors)

L101 ANSWER 5 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **1999:595190** HCAPLUS
DN **131:227661**
ED Entered STN: 21 Sep 1999
TI Modified **factor VIII**
IN Lollar, John S.
PA Emory University, USA
SO PCT Int. Appl., 187 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C07H021-00
ICS C07K014-755; C12N015-11; C12N015-12
CC 15-2 (Immunochemistry)
Section cross-reference(s): 3, 14
FAN.CNT 12

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9946274	A1	19990916	WO 1999-US5193	19990310	<--
	W: AU, CA, CN, CZ, HU, IL, JP, KR, MX, NO, NZ, PL, RU					
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
	US 6180371	B1	20010130	US 1998-37601	19980310	<--
	CA 2322508	AA	19990916	CA 1999-2322508	19990310	<--
	AU 9929956	A1	19990927	AU 1999-29956	19990310	<--
	AU 747644	B2	20020516			
	EP 1062224	A1	20001227	EP 1999-911272	19990310	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
	JP 2002506076	T2	20020226	JP 2000-535651	19990310	<--
	NZ 506771	A	20021126	NZ 1999-506771	19990310	<--
	NO 2000004497	A	20001107	NO 2000-4497	20000908	<--
PRAI	US 1998-37601	A	19980310	<--		
	US 1996-670707	A2	19960626	<--		
	WO 1999-US5193	W	19990310			

AB Specific **amino acid** loci of human **factor VIII** interact with inhibitory **antibodies** of **hemophilia** patients who have developed such **antibodies** after being treated with **factor VIII**. Modified **factor VIII** is disclosed in which the **amino acid** sequence is changed by a substitution at one or more of the specific loci. The modified **factor VIII** may be hybrid

of human and porcine **factor VIII**. The modified **factor VIII** is not inhibited by inhibitory **antibodies** against the **A2** or **C2** domain epitopes. The modified **factor VIII** is useful for treating uncontrollable bleeding in **hemophiliacs**, either to avoid or prevent the action of inhibitory **antibodies**.

ST modified porcine human **factor VIII hemophilia**

IT **Hemophilia**
(**A**; modified and/or hybrid human and porcine **factor VIII** for preventing uncontrollable bleeding in **hemophiliacs** without provoking inhibitory **antibodies**)

IT Blood-coagulation factors
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(PCA (procoagulant activity); modified and/or hybrid human and porcine **factor VIII** for preventing uncontrollable bleeding in **hemophiliacs** without provoking inhibitory **antibodies**)

IT **Antibodies**
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(autoantibodies, inhibitory; modified and/or hybrid human and porcine **factor VIII** for preventing uncontrollable bleeding in **hemophiliacs** without provoking inhibitory **antibodies**)

IT **Antibodies**
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(inhibitory; modified and/or hybrid human and porcine **factor VIII** for preventing uncontrollable bleeding in **hemophiliacs** without provoking inhibitory **antibodies**)

IT **Hemophilia**
Molecular cloning
Protein sequences
cDNA sequences
(modified and/or hybrid human and porcine **factor VIII** for preventing uncontrollable bleeding in **hemophiliacs** without provoking inhibitory **antibodies**)

IT DNA
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(modified and/or hybrid human and porcine **factor VIII** for preventing uncontrollable bleeding in **hemophiliacs** without provoking inhibitory **antibodies**)

IT Hemorrhage
(uncontrollable; modified and/or hybrid human and porcine **factor VIII** for preventing uncontrollable bleeding in **hemophiliacs** without provoking inhibitory **antibodies**)

IT 153065-59-9 201874-16-0 201874-17-1 201874-18-2 201874-19-3
244060-57-9 244060-64-8 244065-54-1 244065-55-2 244065-56-3
RL: PRP (Properties)
(**amino acid** sequence; modified and/or hybrid human and porcine **factor VIII** for preventing uncontrollable bleeding in **hemophiliacs** without provoking inhibitory **antibodies**)

IT **113189-02-9DP, Factor VIII**, analogs
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(modified and/or hybrid human and porcine **factor VIII** for preventing uncontrollable bleeding in **hemophiliacs** without provoking inhibitory **antibodies**)

IT 140742-96-7 201874-20-6 201874-21-7 201874-22-8 201874-23-9
201874-76-2 243905-33-1 244065-57-4 244065-58-5 244065-59-6
RL: PRP (Properties)
(nucleotide sequence; modified and/or hybrid human and porcine **factor VIII** for preventing uncontrollable bleeding in **hemophiliacs** without provoking inhibitory **antibodies**)
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Eaton, D; Biochemistry 1986, V25(26), P8343 HCAPLUS
(2) Lollar; US 5663060 A 1997 HCAPLUS
(3) Pittman; US 5563045 A 1996 HCAPLUS
(4) Scandella, D; Blood 1995, V86(5), P1811 HCAPLUS

L101 ANSWER 6 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **1999:404859** HCAPLUS
DN **131:57772**
ED Entered STN: 01 Jul 1999
TI Methods to treat undesirable immune responses
IN Conti-Fine, Bianca M.
PA Regents of the University of Minnesota, USA
SO PCT Int. Appl., 221 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K039-00
CC 15-2 (Immunochemistry)
Section cross-reference(s): 2, 3
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9930736	A2	19990624	WO 1998-US26787	19981216 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2315537	AA	19990624	CA 1998-2315537	19981216 <--
AU 9931799	A1	19990705	AU 1999-31799	19981216 <--
EP 1037663	A2	20000927	EP 1998-967008	19981216 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRAI US 1997-991143	A2	19971216 <--		
WO 1998-US26787	W	19981216		

AB Isolated and purified **peptides** and variants thereof, useful to prevent or treat **antibody**-mediated diseases, or indications caused by an undesirable **antibody** response to a given antigen, are provided. Also provided are **peptides** and methods useful to prevent or treat indications associated with the use of viral vectors in gene replacement therapy. Further, a method to inhibit or prevent aberrant immune responses to exogenous, non-infectious antigen is provided. The antigen associated with the **antibody**-mediated disease is an endogenous antigen such as acetylcholine receptor, insulin, growth hormone, **factor VIII** or factor IX; or an exogenous antigen such as fungal antigen, plant antigen, domestic cat antigen or mite allergen. The **antibody**-mediated disease is an autoimmune disease, allergic disease, systemic lupus erythematosus, pemphigus, thrombic thrombocytopenic purpura, **hemophilia A**, **hemophilia B**, or myasthenia gravis.
ST antigen T cell epitope **antibody** disease; autoimmune disease

allergy T cell epitope; acetylcholine receptor epitope myasthenia gravis; **factor VIII** IX epitope **hemophilia**; gene therapy recombinant retrovirus adenovirus vector

IT **Hemophilia**
(**A**; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT Cell activation
(**B** cell, inhibitor; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT **Hemophilia**
(**B**; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT **Immunoglobulins**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(G1; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT **Immunoglobulins**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(**G**; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT Animal
(SCID; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT Allergy
Animal virus
Autoimmune disease
Bacteria (Eubacteria)
CD4-positive T cell
Cystic fibrosis
Drugs
Epitopes
Gene therapy
Hemophilia
Hemorrhage
Immune tolerance
Immunosuppressants
Infection
Mammal (Mammalia)
Myasthenia gravis
Plasmapheresis
Respiratory tract
T cell (lymphocyte)
Virus vectors
(T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT **Antibodies**
Antigens
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT Allergens
Cholinergic receptors
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT Muscle, disease
(animal model; T cell epitope of endogenous or exogenous antigen for

treating undesired **antibody**-mediated diseases)
IT Disease, animal
(**antibody**-mediated; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)
IT Cat (Felis catus)
Fungi
Mite and Tick
Plant (Embryophyta)
(antigen; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)
IT **Antibodies**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(autoantibodies; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)
IT Antigens
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(autoantigens; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)
IT Disease, animal
(deficiency; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)
IT T cell (lymphocyte)
(helper cell/inducer, TH2, down-regulation; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)
IT Hematopoietic precursor cell
(human; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)
IT Drug delivery systems
(injections, s.c.; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)
IT Diabetes mellitus
(insulin-dependent; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)
IT Drug delivery systems
(nasal; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)
IT Disease models
(non-human mammalian; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)
IT Skin, disease
(pemphigus; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)
IT Virus
(recombinant; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)
IT Immunodeficiency
(severe combined, animal; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)
IT Lupus erythematosus
(systemic; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)
IT Purpura (disease)
(thrombocytopenic, thrombic; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)
IT Adenoviridae
Retroviridae
(vector; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)
IT **Proteins, general, biological studies**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(virus-specific; T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT 9001-28-9, Factor IX 9002-72-6, Growth hormone 9004-10-8, Insulin, biological studies **109319-16-6, Factor VIII**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

IT 9026-93-1, Adenosine deaminase
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(T cell epitope of endogenous or exogenous antigen for treating undesired **antibody**-mediated diseases)

L101 ANSWER 7 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1998:219210 HCAPLUS
DN 128:317097
ED Entered STN: 18 Apr 1998
TI A human alloantibody interferes with binding of factor IXa to the **factor VIII** light chain
AU Fijnvandraat, Karin; Celie, Patrick H. N.; **Turenhout, Ellen A. M.**; ten Cate, Jan W.; Van Mourik, Jan A.; Mertens, Koen; Peters, Marjolein; **Voorberg, Jan**
CS Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Departments of Blood Coagulation and Plasma Protein Technology, Amsterdam, 1066 CX, Neth.
SO Blood (**1998**), 91(7), 2347-2352
CODEN: BLOOAW; ISSN: 0006-4971
PB W. B. Saunders Co.
DT Journal
LA English
CC 1-8 (Pharmacology)
AB Inhibitory **antibodies** directed against **factor VIII** develop in a substantial number of patients with **hemophilia A** as a consequence of **factor VIII** replacement therapy. These **antibodies** usually recognize discrete epitopes within the **A2** and/or the **C2** domains of **factor VIII**. Here, the authors have characterized the **antibodies** present in the plasma of a patient affected by severe **hemophilia A**. The **antibodies** reacted readily with the metabolically labeled **factor VIII** light chain and fragments thereof when analyzed by immunopptn. The inhibitory activity could be neutralized by the complete light chain, whereas only slight neutralization occurred with a fragment comprising the isolated **C2** domain. Binding of the majority of **antibodies** to in vitro synthesized **factor VIII** fragments was dependent on the presence of **amino acid** residues Gln1778-Met1823, a region known to contain a factor IXa binding site. Functional characterization showed that purified **IgG** from the patient's serum inhibited binding of factor IXa to immobilized **factor VIII** light chain in a dose-dependent manner. These data indicate that human alloantibodies may inhibit **factor VIII** activity by interfering with factor IXa-factor VIIIa complex assembly.
ST alloantibody coagulation factor IXa VIII
IT **Hemophilia**
(**A**; human alloantibody interferes with binding of coagulation factor IXa to **factor VIII** light chain)
IT **Immunoglobulins**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**G**; human alloantibody interferes with binding of coagulation factor IXa to **factor VIII light**

chain)
IT **Antibodies**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (alloantibodies; human alloantibody interferes with binding of coagulation factor IXa to **factor VIII** light chain)
IT Drug resistance
(human alloantibody interferes with binding of coagulation factor IXa to **factor VIII** light chain)
IT 37316-87-3, Blood coagulation factor IXa
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(human alloantibody interferes with binding of coagulation factor IXa to **factor VIII** light chain)
IT **109319-16-6, Blood-coagulation factor VIII**
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(human alloantibody interferes with binding of coagulation factor IXa to **factor VIII** light chain)
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L101 ANSWER 8 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **1997:718000** HCAPLUS
DN **127:356538**
ED Entered STN: 13 Nov 1997
TI construction of inactivation resistant **factor VIII** procoagulant and applications to **hemophilia** treatment
IN Kaufman, Randal J.; Pipe, Steven W.; Amano, Kagehiro
PA Regents of the University of Michigan, USA; Kaufman, Randal J.; Pipe, Steven W.; Amano, Kagehiro
SO PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DT Patent

LA English
IC ICM C12N009-48
ICS C12N015-63; C12N001-21; C07H021-04; A61K038-48; A61K039-395
CC 7-5 (Enzymes)
Section cross-reference(s): 14
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9740145	A1	19971030	WO 1997-US6563	19970424 <--
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9732027	A1	19971112	AU 1997-32027	19970424 <--
	EP 910628	A1	19990428	EP 1997-927596	19970424 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2000511407	T2	20000905	JP 1997-538216	19970424 <--
	US 2003148953	A1	20030807	US 2002-283648	20021029 <--
PRAI	US 1996-16117P	P	19960424 <--		
	US 1996-17785P	P	19960515 <--		
	WO 1997-US6563	W	19970424 <--		
	US 1997-980038	B1	19971126 <--		
	US 2001-819098	A2	20010411		
	US 2002-122264	A2	20020411		

AB Novel purified and isolated nucleic acid sequences encoding procoagulant-active **FVIII proteins** are described. To determine whether specific **amino acid** sequences within **FVIII** A-domain inhibit secretion, chimeric **proteins** containing the **A1** and **A2**-domains of **FVIII** or **FV** were studied. The nucleic acid sequences of encode **amino acid** sequences corresponding to known human **FVIII** sequences where residue Phe309 is mutated. The nucleic acid sequences also encode human **FVIII** sequences where the APC cleavage sites, Arg336 and Ile562, are mutated. The nucleic acid sequences of sequences corresponding to known human **FVIII** sequences where the **B**-domain is deleted, the **von Willebrand factor** binding site is deleted, a thrombin cleavage site is mutated and an **amino acid** sequence spacer is inserted between the **A2**- and **A3**-domains. These nucleotide encode **factor VIII proteins** capable of secretion at levels higher than typically obtained with wild-type **factor VIII**. Methods of producing the **FVIII proteins** and pharmaceutical compns. containing the nucleotide sequences or **proteins** as well as methods of treating patients suffering from **hemophilia** are also provided. A lower dosage of **protein** may be administered to the **hemophiliac** patient during **FVIII** replacement therapy. By utilizing the **proteins** described, the total exposure of **protein** to the patient is reduced, thereby lowering the likelihood of inhibitor formation.

ST inactivation resistant **factor VIII** procoagulant **hemophilia**

IT **Antibodies**
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(anti-light chain **antibody** ESH8 [inducing **FVIII** binding to vWF used to stabilize inactivation resistant **FVIII**

]; 2248-2285 procoagulant epitope recognition; construction of inactivation resistant **factor VIII** procoagulant)

IT **Hemophilia**
(applications for treatment of; construction of inactivation resistant **factor VIII** procoagulant and applications to **hemophilia** treatment)

IT Drug delivery systems
Gene therapy
Secretion (process)
(construction of inactivation resistant **factor VIII** procoagulant and applications to **hemophilia** treatment)

IT Epitopes
(epitope of 2248 to 2285 of **Blood-coagulation factor VIII** procoagulant; **antibody** recognizing; construction of inactivation resistant **factor VIII** procoagulant and applications to **hemophilia** treatment)

IT Crosslinking
(inducing **FVIII** binding to vWF used to stabilize inactivation resistant **FVIII**; construction of inactivation resistant **factor VIII** procoagulant and applications to **hemophilia** treatment)

IT **Proteins, specific or class**
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(modified; construction of inactivation resistant **factor VIII** procoagulant and applications to **hemophilia** treatment)

IT **109319-16-6**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(anti-light chain **antibody** ESH8 and crosslinkers inducing **FVIII** binding to vWF; construction of inactivation resistant **factor VIII** procoagulant and applications to **hemophilia** treatment)

IT 42617-41-4, Activated **protein** c
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(generation of **protein** resistant to cleavage by; construction of inactivation resistant **factor VIII** procoagulant and applications to **hemophilia** treatment)

IT **113189-02-9DP**, derivs
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(modified **peptides** of; construction of inactivation resistant **factor VIII** procoagulant and applications to **hemophilia** treatment)

IT 9002-04-4, Thrombin
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(structural and functional stability of IR8 during thrombin cleavage; construction of inactivation resistant **factor VIII** procoagulant and applications to **hemophilia** treatment)

L101 ANSWER 9 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **1997:710503** HCAPLUS
DN **128:31607**
ED Entered STN: 10 Nov 1997
TI Characterization of a genetically engineered inactivation-resistant **coagulation factor VIIIa**
AU Pipe, Steven W.; Kaufman, Randal J.
CS Department of Pediatrics, University of Michigan Medical Center, Ann Arbor, MI, 48109, USA

SO Proceedings of the National Academy of Sciences of the United States of America (**1997**), 94(22), 11851-11856
CODEN: PNASA6; ISSN: 0027-8424
PB National Academy of Sciences
DT Journal
LA English
CC 6-3 (General Biochemistry)

AB Individuals with **hemophilia A** require frequent infusion of prepns. of **coagulation factor VIII**. The activity of **factor VIII** (**FVIII**) as a cofactor for factor IXa in the coagulation cascade is limited by its instability after activation by thrombin. Activation of **FVIII** occurs through proteolytic cleavage and generates an unstable **FVIII** heterotrimer that is subject to rapid dissociation of its subunits. In addition, further proteolytic cleavage by thrombin, factor Xa, factor IXa, and activated **protein** C can lead to inactivation. We have engineered and characterized a **FVIII protein**, IR8, that has enhanced in vitro stability of **FVIII** activity due to resistance to subunit dissociation and proteolytic inactivation. **FVIII** was genetically engineered by deletion of residues 794-1689 so that the **A2** domain is covalently attached to the light chain. Missense mutations at thrombin and activated **protein** C inactivation cleavage sites provided resistance to proteolysis, resulting in a single-chain **protein** that has maximal activity after a single cleavage after arginine-372. The specific activity of partially purified **protein** produced in transfected COS-1 monkey cells was 5-fold higher than wild-type (WT) **FVIII**. Whereas WT **FVIII** was inactivated by thrombin after 10 min in vitro, IR8 still retained 38% of peak activity after 4 h. Whereas binding of IR8 to **von Willebrand factor** (vWF) was reduced 10-fold compared with WT **FVIII**, in the presence of an anti-light chain **antibody**, ESH8, binding of IR8 to vWF increased 5-fold. These results demonstrate that residues 1690-2332 of **FVII** are sufficient to support high-affinity vWF binding. Whereas ESH8 inhibited WT **factor VIII** activity, IR8 retained its activity in the presence of ESH8. We propose that resistance to **A2** subunit dissociation abrogates inhibition by the ESH8 **antibody**. The stable **FVIIIa** described here provides the opportunity to study the activated form of this critical coagulation factor and demonstrates that **proteins** can be improved by rationale design through genetic engineering technol.

ST factor VIIIa von Willebrand binding

IT **Blood-coagulation factors**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(**VIIIa**; characterization of a genetically engineered inactivation-resistant **coagulation factor VIIIa**)

IT **109319-16-6**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(characterization of a genetically engineered inactivation-resistant **coagulation factor VIIIa**)

RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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L101 ANSWER 10 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **1997:413693** HCAPLUS
DN **127:144671**
ED Entered STN: 03 Jul 1997
TI Analysis of **factor VIII** inhibitors using hybrid human/porcine **factor VIII**
AU Lollar, Pete
CS Department Medicine, Emory University, Atlanta, GA, 30322, USA
SO Thrombosis and Haemostasis (**1997**), 78(1), 647-651
CODEN: THHADQ; ISSN: 0340-6245
PB Schattauer
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review with 39 refs. is given on anal. of **factor VIII** inhibitors using hybrid human/porcine **factor VIII**. Recombinant hybrid human/porcine **factor VIII** mols. were used to map a major determinant of the epitope recognized by human anti-**factor VIII A2** domain inhibitory **antibodies** to a region bounded by human **fVIII** residues Arg484-Ile508. This approach is used to characterize the **C2**

domain inhibitor epitope. The process of creating hybrid human/porcine **factor VIII** mols. to map inhibitor epitopes produces procoagulantly active **fVIII** with reduced reactivity with clin. **factor VIII** inhibitors. This suggests that it may be possible to develop of a hybrid human/porcine **factor VIII** that is useful in the management of **hemophilia A** and acquired **hemophilia**.

ST review **factor VIII** inhibitor **amino acid**

IT **Protein sequences**
(anal. of **factor VIII** inhibitors using hybrid human/porcine **factor VIII**)

IT **113189-02-9, Factor VIII**
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(anal. of **factor VIII** inhibitors using hybrid human/porcine **factor VIII**)

L101 ANSWER 11 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1997:394590 HCAPLUS
DN 127:107880
ED Entered STN: 26 Jun 1997
TI The missense mutation Arg593 → Cys is related to **antibody** formation in a patient with mild **hemophilia A**
AU Fijnvandraat, Karin; **Turenhout, Ellen A. M.**; **van den Brink, Edward N.**; ten Cate, Jan W.; van Mourik, Jan A.; Peters, Marjolein; **Voorberg, Jan**
CS Dep. Blood Coagulation, Central Lab. Netherlands Red Cross Blood Transfusion Serv., Amsterdam, 1066 CX, Neth.
SO Blood (**1997**), 89(12), 4371-4377
CODEN: BLOOAW; ISSN: 0006-4971
PB Saunders
DT Journal
LA English
CC 15-8 (Immunochemistry)
Section cross-reference(s): 1
AB The development of inhibitory **antibodies** to **factor VIII** in patients affected by a mild form of **hemophilia A** (**factor VIII** > 0.05 IU/mL) is considered a rare event. In this study, the authors evaluated the relation between genotype and anti-**factor VIII antibody** formation in a patient with mild **hemophilia A**. Mutation anal. showed that a missense mutation in the **factor VIII** gene leading to replacement of Arg593 by Cys in the **A2** domain of **factor VIII** was associated with **hemophilia A** in this patient. The anti-**factor VIII antibodies** present in the patient's plasma were characterized using metabolically labeled **factor VIII** fragments expressed in insect cells. The anti-**factor VIII antibodies**, composed of subclasses IgG2 and **IgG4**, reacted with both the fragment corresponding to the **factor VIII** heavy chain and the **A2** domain. The Arg593 → Cys substitution was introduced into the cDNA encoding the **A2** domain of **factor VIII** and the resulting construct was expressed in insect cells. Strikingly, the metabolically labeled **A2** domain carrying the Arg593 → Cys mutation was not recognized by the anti-**factor VIII antibodies** present in the plasma of the patient. These data indicate that the antifactor VIII **antibodies** are exclusively directed against exogenous **factor VIII**. This strongly suggests that the Arg593 → Cys substitution results in recognition of wild-type **factor VIII** as nonself and is thereby related to the formation of anti-**factor VIII**

antibodies after **factor VIII** replacement therapy in this particular patient.

ST **hemophilia A** missense mutation **antibody** **FVIII; factor VIII** mutation **hemophilia A antibody**

IT **Protein motifs**
(**A2** domain; missense mutation Arg593 → Cys is related to formation of **antibody** against exogenous **factor VIII** but not against mutant **factor VIII** in human with mild **hemophilia A**)

IT **Hemophilia**
(**A**; missense mutation Arg593 → Cys is related to formation of **antibody** against exogenous **factor VIII** but not against mutant **factor VIII** in human with mild **hemophilia A**)

IT Gene, animal
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(F8; missense mutation Arg593 → Cys is related to formation of **antibody** against exogenous **factor VIII** but not against mutant **factor VIII** in human with mild **hemophilia A**)

IT **Immunoglobulins**
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(G2, anti-**factor VIII**; missense mutation Arg593 → Cys is related to formation of **antibody** against exogenous **factor VIII** but not against mutant **factor VIII** in human with mild **hemophilia A**)

IT **Immunoglobulins**
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(**G4**, anti-**factor VIII**; missense mutation Arg593 → Cys is related to formation of **antibody** against exogenous **factor VIII** but not against mutant **factor VIII** in human with mild **hemophilia A**)

IT **Antibodies**
RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(anti-**factor VIII**; missense mutation Arg593 → Cys is related to formation of **antibody** against exogenous **factor VIII** but not against mutant **factor VIII** in human with mild **hemophilia A**)

IT Genotypes
(missense mutation Arg593 → Cys is related to formation of **antibody** against exogenous **factor VIII** but not against mutant **factor VIII** in human with mild **hemophilia A**)

IT Mutation
(missense, R593C; missense mutation Arg593 → Cys is related to formation of **antibody** against exogenous **factor VIII** but not against mutant **factor VIII** in human with mild **hemophilia A**)

IT **113189-02-9, Coagulation factor VIIIc**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BPR (Biological

process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); PROC (Process); USES (Uses)
(missense mutation Arg593 → Cys is related to formation of **antibody** against exogenous **factor VIII** but not against mutant **factor VIII** in human with mild **hemophilia A**)

L101 ANSWER 12 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **1997:317203** HCAPLUS
DN **127:3893**
ED Entered STN: 17 May 1997
TI Identification of novel **factor VIII** inhibitor epitopes using synthetic **peptide** arrays
AU Palmer, Douglas S.; Dudani, Anil K.; Drouin, Jeanne; Ganz, Peter R.
CS Ottawa Centre, Canadian Red Cross Society, Blood Services, University of Ottawa, Can.
SO Vox Sanguinis (**1997**), 72(3), 148-161
CODEN: VOSAAD; ISSN: 0042-9007
PB Karger
DT Journal
LA English
CC 15-2 (Immunochemistry)
AB Mapping the **antibody**-binding sites on the **factor VIII** (**FVIII**) **protein** opens the prospect of studying the development of **FVIII** inhibitors and the alteration of inhibitor specificities over time. This paper describes a novel approach to the mapping of **FVIII antibody**-binding sites. Immobilized synthetic **peptide** arrays covering 80% of the complete 2351 **amino acid** sequence of **factor VIII** (**FVIII**) were used to determine epitope specificity of 6 alloantibodies and 3 autoantibodies inhibitory to **FVIII** activity. This detailed assessment was carried out using a modified ELISA with plasma from normal persons or **hemophilia A** patients without inhibitors as neg. controls. **Antibody** -combining sites could be differentiated in both a qual. and quant. manner and were patient-specific. Highly reactive **peptides** were restricted to specific sites in the **A1-A3** and **C1-C2** domains and were not proximal to known proteolytic cleavage sites. Free **peptides** incubated in vitro with the plasmas of 3 patients significantly reduced residual inhibitor titers in a dose-dependent manner. This technique permits the study of the development and specificity of **FVIII** inhibitors, can detect and differentiate between inhibitory and noninhibitory **antibodies** using immobilized or free **peptides**, resp., permits correlation of **antibody**-combining sites with inhibition of **FVIII** activity and provides a basis for the development of inhibitor adsorption or neutralization technol.
ST **factor VIII** epitope mapping inhibitor **antibody**
IT **Antibodies**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(alloantibodies; identification of novel **factor VIII** epitopes recognized by inhibitor **antibodies** using synthetic **peptide** arrays)
IT **Antibodies**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(autoantibodies; identification of novel **factor VIII** epitopes recognized by inhibitor **antibodies** using synthetic **peptide** arrays)
IT Epitopes
(identification of novel **factor VIII** epitopes

recognized by inhibitor **antibodies** using synthetic **peptide** arrays)

IT **Peptides, biological studies**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(identification of novel **factor VIII** epitopes recognized by inhibitor **antibodies** using synthetic **peptide** arrays)

IT Epitopes
(mapping; identification of novel **factor VIII** epitopes recognized by inhibitor **antibodies** using synthetic **peptide** arrays)

IT **113189-02-9, Factor VIII**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(identification of novel **factor VIII** epitopes recognized by inhibitor **antibodies** using synthetic **peptide** arrays)

L101 ANSWER 13 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **1997:277036** HCAPLUS
DN **127:49146**
ED Entered STN: 30 Apr 1997
TI Autoantibody selectively inhibits binding of **von Willebrand factor** to **glycoprotein** Ib. Recognition site is located in the **A1** loop of **von Willebrand factor**
AU Mohri, Hiroshi; Yamazaki, Etsuko; Suzuki, Zekou; Takano, Toshikuni; Yokota, Shumpei; Okubo, Takao
CS School Medicine, Yokohama City Univ., Yokohama, 236, Japan
SO Thrombosis and Haemostasis (**1997**), 77(4), 760-766
CODEN: THHADQ; ISSN: 0340-6245
PB Schattauer
DT Journal
LA English
CC 15-8 (Immunochemistry)
Section cross-reference(s): 7
AB In a severe von Willebrand disease an inhibitor was suggested directed against vWF:RCo activity of **von Willebrand factor** (vWF) without inhibition of the **FVIII**:C. The inhibitor was identified as an **antibody** of **IgG** class. The inhibitor inhibited the interaction of vWF in the presence of ristocetin and that of asialo-vWF with GPIb while it partially blocked botrocetin-mediated interaction of vWF to GPIb. The inhibitor reacted with native vWF, the 39/34kDa fragment (**amino acids** [aa] 480/481-718) and the recombinant vWF fragment (MalE-rvWF508-704), but not with Fragment III-T2 (heavy chains, aa 273-511; light chains, aa 674-728). A synthetic **peptide** (aa 514-542) did not inhibit vWF-inhibitor complex formation. It was concluded that this is the 1st autoantibody of class **IgG** from human origin that recognizes the sequence in the **A1** loop of vWF, resulting in a virtual absence of functional vWF and a concomitant severe bleeding tendency although recognition site is different from the residues 514-542 which is crucial for vWF-GPIb interaction.
ST autoantibody **IgG** von Willebrand disease
IT **Glycolipoproteins**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(GPIb; **IgG** autoantibody to the **glycoprotein** Ib binding domain of **von Willebrand factor** in a human with von Willebrand disease)

IT Enzyme functional sites
Von Willebrand's disease
(**IgG** autoantibody to the **glycoprotein** Ib binding domain of **von Willebrand factor** in a

human with von Willebrand disease)
IT **Immunoglobulins**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(autoantibodies, **G**; **IgG** autoantibody to the **glycoprotein** Ib binding domain of **von Willebrand factor** in a human with von Willebrand disease)
IT Conformation
(**protein**; **IgG** autoantibody to the **glycoprotein** Ib binding domain of **von Willebrand factor** in a human with von Willebrand disease)
IT **109319-16-6**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**IgG** autoantibody to the **glycoprotein** Ib binding domain of **von Willebrand factor** in a human with von Willebrand disease)

L101 ANSWER 14 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **1995:540270** HCAPLUS
DN **122:288519**
ED Entered STN: 10 May 1995
TI Selection and application of human single chain **Fv** **antibody** fragments from a semi-synthetic phage **antibody** display library with designed **CDR3** regions
AU Kruif, John De; Boel, Edwin; Logtenberg, Ton
CS Dep. of Immunology and Eykman-Winkler, Univ. of Utrecht, Utrecht, 3508 GA, Neth.
SO Journal of Molecular Biology (**1995**), 248(1), 97-105
CODEN: JMOBAK; ISSN: 0022-2836
PB Academic
DT Journal
LA English
CC 15-3 (Immunochemistry)
Section cross-reference(s): 3
AB The authors have constructed a large (3.6+108 clones) phage display library of human single chain **Fv** (**scFv**) **antibody** fragments by combining 49 germline VH genes with synthetic heavy chain **CDR3** (HCDR3) regions and seven light chains. The HCDR3 regions varied in length between 6 and 15 residues and were designed to contain fully randomized stretches of **amino acid** residues flanked by regions of limited residue variability that were composed of **amino acid** residues that frequently occur in natural **antibodies**. This approach should increase the frequency of functional mols. in the library and, in addition, make it possible to efficiently utilize available cloning space. By direct selection on solid phase-bound antigens were obtained phage **antibodies** with binding activities to 13 different antigens, including **Von Willebrand factor**, the DNA-binding HMG box of transcription factor TCF-1 and the tumor antigen EGP-2. In addition, a competitive selection procedure was applied to target phage **antibodies** to the desired portion of a recombinant fusion **protein** and to select phage **antibodies** capable of discriminating between the two highly homologous homeobox **proteins** PBX1a and PBX2. The functional capacity of monoclonal phage **antibodies** was assessed in immuno-histochem. staining of tissue specimens, Western blotting assays and immunofluorescent anal. of cells by flow cytometry. The results demonstrate that this large human phage **antibody** library contains a broad assortment of binding specificities that can be applied in a variety of biochem. assays.
ST **antibody Fv** fragment phage library
IT Antigens

RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(EGP-2; **antibodies** from phage display library of human single chain **Fv antibody** fragments binding to)

IT Combinatorial library
Virus, bacterial
(phage display library of human single chain **Fv antibody** fragments)

IT **Antibodies**
RL: BPN (Biosynthetic preparation); PRP (Properties); BIOL (Biological study); PREP (Preparation)
(phage display library of human single chain **Fv antibody** fragments)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(phage display library of human single chain **Fv antibody** fragments)

IT Ribonucleic acid formation factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(TCF-1 (T-cell factor 1), **antibodies** from phage display library of human single chain **Fv antibody** fragments binding to)

IT **109319-16-6**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**antibodies** from phage display library of human single chain **Fv antibody** fragments binding to)

L101 ANSWER 15 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **1995:531444** HCAPLUS
DN **123:53000**
ED Entered STN: 06 May 1995
TI A 110-amino acid region within the A1-domain of **coagulation factor VIII** inhibits secretion from mammalian cells
AU Marquette, Kimberly A.; Pittman, Debra D.; Kaufman, Randal J.
CS Howard Hughes Med. Inst., Univ. Michigan Med. Cent., Ann Arbor, MI, 48105, USA
SO Journal of Biological Chemistry (**1995**), 270(17), 10297-303
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
CC 13-5 (Mammalian Biochemistry)
AB **Factor VIII** is the coagulation factor deficient in the X-chromosome-linked bleeding disorder **hemophilia** A. **Factor VIII** is homologous to blood coagulation factor V, both having a domain structure of A1-A2-B-A3-C1-C2. Previous transfection studies demonstrated that **factor VIII** is 10-fold less efficiently expressed than the homologous coagulation factor, factor V. The inefficient expression correlated with interaction of the **factor VIII** primary translation product with the protein chaperonin BiP in the lumen of the endoplasmic reticulum. In contrast, factor V was not detected in association with BiP and was secreted efficiently. To **determine** whether specific amino acid sequences within **factor VIII** inhibit secretion, we have studied the secretion of **factor VIII** deletion and **factor VIII**/factor V chimeric proteins upon transient transfection of COS-1 monkey cells. A chimeric **factor VIII** protein that contained the A1- and A2-domains of factor V was secreted with a similar efficiency as wild-type factor V, whereas the **complementary** chimera having the A1- and A2-domains of **factor VIII** was secreted with low efficiency, similar to

wild-type **factor VIII**. These results suggested that sequences within the A1- and A2-domains were responsible for the low secretion efficiency of **factor VIII**. Secretion of A1-domain-deleted **factor VIII** was increased approx. 10-fold compared to wild-type **factor VIII** or A2-domain-deleted **factor VIII**. Expression of the **factor VIII** A1-domain alone did not yield secreted protein, whereas expression of the **factor VIII** A2-domain alone or the factor V A1-domain or A2-domain alone directed synthesis of secreted protein. Secretion of a hybrid in which the carboxyl-terminal 110 amino acids of the A1-domain were replaced by homologous sequences from the factor V A1-domain was also increased 10-fold compared to wild-type **factor VIII**, however, the secreted protein was not functional and the heavy and light chains were not associated These results localize a 110-amino acid **region** within the A1-domain that inhibits **factor VIII** secretion. This **region** is clustered with multiple short peptide sequences that have potential to bind BiP.

ST **coagulation factor VIII** domain secretion chaperonin; **blood coagulation factor VIII** secretion chaperonin; protein BiP **coagulation factor VIII** secretion

IT Endoplasmic reticulum
(110-amino acid region within A1-domain of **coagulation factor VIII** inhibits secretion from mammalian cells)

IT **Hemophilia**
(**A**, 110-amino acid region within A1-domain of **coagulation factor VIII** inhibits secretion from mammalian cells)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(GRP78 (glucose-regulated protein, 78,000-mol-weight), 110-amino acid region within A1-domain of **coagulation factor VIII** inhibits secretion from mammalian cells)

IT Biological transport
(secretion, 110-amino acid region within A1-domain of **coagulation factor VIII** inhibits secretion from mammalian cells)

IT 9001-24-5, Blood Coagulation factor V **113189-02-9** 164641-21-8
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(110-amino acid region within A1-domain of **coagulation factor VIII** inhibits secretion from mammalian cells)

L101 ANSWER 16 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **1994:503079** HCAPLUS
DN **121:103079**
ED Entered STN: 03 Sep 1994
TI Chimeric blood coagulation **proteins**
IN Kane, William H.; Ortel, Thomas L.
PA Duke University, USA
SO PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K037-00
ICS C07K013-00; C12N005-10; C12N005-12; C12N015-62; C12N015-79; G01N033-53
CC 7-2 (Enzymes)
Section cross-reference(s): 1
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI	WO 9411013	A1	19940526	WO 1993-US10931	19931111 <--
	W: AU, CA, JP				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9456023	A1	19940608	AU 1994-56023	19931111 <--
	US 5587310	A	19961224	US 1994-273362	19940711 <--
PRAI	US 1992-975839		19921113 <--		
	WO 1993-US10931		19931111 <--		

AB Chimeric blood coagulation **proteins** for use in the treatment of **hemophilia** and in the mapping of epitopes of the factors are described. The **proteins** are either coagulation factor V in which at least one of the **A3**, **C1** or **C2** domain exons is replaced with the homologous exon of **coagulation factor VIII**; or **coagulation factor VIII** in which at least one of the **A3**, **C1** or **C2** domain exons is replaced with the homologous exon of coagulation factor V. The construction and expression of genes for several such analogs is described.

ST chimeric blood coagulation factor V VIII

IT Blood analysis
Immunoassay
(for **antibodies** inhibiting blood coagulation factors, detection of, fusion **proteins** of coagulation factors V and VIII for)

IT **Antibodies**
RL: BIOL (Biological study)
(inhibiting blood coagulation factors, detection of, fusion **proteins** of coagulation factors V and VIII for)

IT **Hemophilia**
(treatment of, domain exchange fusion **proteins** of coagulation factors V and VIII for, minimization of immune response in relation to)

IT **Antibodies**
RL: BIOL (Biological study)
(allo-, inhibiting blood coagulation factors, detection of, fusion **proteins** of coagulation factors V and VIII for)

IT Gene, animal
RL: BIOL (Biological study)
(chimeric, for domain-exchange fusion products of human blood coagulation factors V and VIII, expression in animal cell culture of)

IT 9001-24-5D, Blood-coagulation factor V, fusion products with **factor VIII 9001-27-8D, Blood-coagulation factor VIII**, fusion products with factor V
RL: BIOL (Biological study)
(domain exchange in, chimeric gene for, expression in animal; cell culture of, for treatment of **hemophilia** and prophylaxis of alloimmunity)

L101 ANSWER 17 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **1988:156310** HCAPLUS
DN **108:156310**
ED Entered STN: 30 Apr 1988
TI F VIII subunits: purification and antigenic properties
AU Nordfang, Ole; Ezban, Mirella; Hansen, Jan J.
CS Nord. Gentofte A/S, Gentofte, Den.
SO Thrombosis and Haemostasis (**1987**), 58(4), 1043-8
CODEN: THHADQ; ISSN: 0340-6245
DT Journal
LA English
CC 63-3 (Pharmaceuticals)
Section cross-reference(s): 13

AB **Factor VIII**-light chain (**FVIII**-LC) and **FVIII**-Heavy chain (**FVIII**-HC) were purified from human

plasma using immunosorbents containing monoclonal **antibodies** or human inhibitor **antibodies**. **FVIII**-LC was subsequently isolated in essentially pure state by cation exchange chromatog. The prepns. obtained contained 50 ng of **protein** for each unit of **FVIII**-LC antigen (**FVIII**-LC:Ag). Affinity purified **FVIII**-LC and **FVIII**-HC prepns. containing <0.3% of the opposite subunit were added in **FVIII**:C inhibition assay of **hemophilia A** inhibitor **antibodies**. **FVIII**-C was able to fully block the inhibitor activity in 6 out of 7 **hemophilia A** plasmas and partially block the inhibitor activity of one plasma. **FVIII**-HC only blocked **FVIII**:C inhibiting **antibodies** form the plasma that was not fully blocked by **FVIII**-LC. **FVIII**-LC can be used for immunotherapy of the patients whose **FVIII**:C inhibiting **antibodies** are directed towards **FVIII**-LC. When **FVIII**-LC was coupled to Sepharose at a concentration of 4800 units of **FVIII**-LC:Ag per mL Sepharose, 0.2 mL of the immunosorbent was able to bind 900 Bethesda units from 100 mL **hemophilia A** inhibitor plasma. This opens the possibility to remove **FVIII** inhibitor **antibodies** from circulation by extracorporeal immunotherapy with **FVIII**-LC coupled to Sepharose.

ST **blood coagulation factor VIII**
purifn; antigenicity **factor VIII**

IT Circulation
(extracorporeal, **factor VIII** inhibitor **antibodies** removal in, by immunoadsorption)

IT **Antibodies**
RL: BIOL (Biological study)
(monoclonal, immunosorbents containing, for purification of **blood coagulation factor VIII**)

IT 9012-36-6D, reaction products with **factor VIII**
113189-02-9D, reaction products with Sepharose
RL: BIOL (Biological study)
(**blood coagulation factor VIII** inhibitor **antibodies** removal by)

IT **113189-02-9P**
RL: PREP (Preparation)
(purification and antigenic properties of)

L101 ANSWER 18 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **1986:539598** HCAPLUS
DN **105:139598**
ED Entered STN: 18 Oct 1986
TI Preparation for the treatment of **hemophilia A** inhibitor patients
IN Nordfang, Ole; Rasmussen, Mirella Ezban
PA Nordisk Gentofte, Den.
SO PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K037-02
ICS A61K037-04; A61K035-16; C07K015-06
CC 63-3 (Pharmaceuticals)
Section cross-reference(s): 1, 18
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 8602838	A1	19860522	WO 1985-DK105	19851105 <--
	W: AU, DK, FI, JP, NO, US				
	RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
	CA 1269042	A1	19900515	CA 1985-494555	19851104 <--
	IL 76929	A1	19900726	IL 1985-76929	19851104 <--

AU 8550926	A1	19860603	AU 1985-50926	19851105	<--
AU 599310	B2	19900719			
EP 201574	A1	19861120	EP 1985-905784	19851105	<--
EP 201574	B1	19911127			
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE					
ES 549115	A1	19861201	ES 1985-549115	19851105	<--
JP 62501006	T2	19870423	JP 1985-505194	19851105	<--
AT 69727	E	19911215	AT 1985-905784	19851105	<--
US 4831119	A	19890516	US 1986-881687	19860620	<--
DK 8603180	A	19860704	DK 1986-3180	19860704	<--
DK 165940	B	19930215			
DK 9000418	A	19900216	DK 1990-418	19900216	<--
DK 173863	B1	20020107			
PRAI DK 1984-5253	A	19841105	<--		
EP 1985-905784	A	19851105	<--		
WO 1985-DK105	A	19851105	<--		

AB A composition for the treatment of **hemophilia A** inhibitor patients, those who develop **antibodies** against **Factor VIII**:C, comprises a **protein** or **peptide** having a specific **Factor VIII**:CAg activity of ≥0.5 U/mg **protein** characterized by a ratio of **Factor VIII**:CAg to **Factor VIII**:C procoagulant activities of 5-10:1. A fragment of **Factor VIII**:C, which displays a doublet of a mol. weight of 80/77 kD in electrophoresis, is the reactive **hemophilia A** inhibitor **antibodies** and has VIII:CAg activity. This fragment and more low-mol.-weight fragments of **Factor VIII**:C are capable of neutralizing the coagulation inhibiting effect of all tested **antibodies**. Such fragments can therefore be used as active component in prepns. for providing immunotolerance towards **Factor VIII**:C in high-dose treatment of inhibitor patients. The **peptides** are useful as an immunosorbent in specific extracorporeal adsorption treatment of inhibitor patients. The inhibitor reactive **peptides** can be recovered from plasma fractions by affinity chromatog., hydrophobic interaction chromatog. or cation exchange or they may be produced biosynthetically and recovered in a similar manner. **IgG** was coupled to Sepharose 4B activated with CNBr, blocked with glycine, washed with buffers, and the gel incubated with AHF. The gel was washed on a column with buffer and eluted with the buffer to give an eluate containing VIII:CAg.

ST **hemophilia A** inhibitor factor VIIIC

IT **Hemophilia**
(**A**, inhibitor patients, treatment of, with **blood coagulation factor VIII**:CAg and **factor VIII**:C)

IT **Immunoglobulins**
RL: PREP (Preparation)
(**G, blood coagulation factor VIII**:CAg preparation of, for treatment of **hemophilia A** inhibitor patients)

IT **9001-27-8P**
RL: PREP (Preparation)
(clotting antigen and blood coagulant activity of, preparation and treatment of **hemophilia A** inhibitor patients with)

L101 ANSWER 19 OF 19 HCAPLUS COPYRIGHT 2003 ACS on STN
AN **1979:454297** HCAPLUS
DN **91:54297**
ED Entered STN: 12 May 1984
TI Rapid isolation and purification of **antibody** to **Factor VIII** by **protein** A
AU Lee, Helen; Tucker, Derek; Allain, J. P.
CS Oxford Haemophilia Cent., Churchill Hosp., Oxford, UK

SO Thrombosis Research (**1979**), 14(6), 925-30
CODEN: THBRAA; ISSN: 0049-3848
DT Journal
LA English
CC 15-1 (Immunochemistry)
AB A simple and reproducible method was developed for rapidly isolating and purifying **antibodies** to **blood-coagulation Factor VIII** from the plasma of both **hemophilic** and nonhemophilic patients. The 1-step separation of these **Igs** makes use of the high affinity binding of **protein** A with the Fc region of the human IgG1, IgG2, and **IgG4** subclasses but not with the IgG3 subclass. Small **protein** A-Sepharose CL-4B gel columns were used to isolate the **IgG** subclasses which contain the anti-**Factor VIII** activity from as little as 0.5 mL of plasma. The yield of the **antibody** was 70-80%. When the purification procedure was combined with a solid phase agarose gel assay for **antibody** to **factor VIII**, a large number of samples could be tested and only small amts. of patient's plasma were required. The plasma of a patient with **antibody** to factor V was also fractionated by **protein** A with similar results.
ST **protein** A **factor VIII antibody**; staphylococcal **protein** A **antibody factor VIII**; **coagulation factor VIII antibody** isolation
IT' Staphylococcus aureus
(**protein** A of, in **blood-coagulation factor VIII antibody** isolation and purification)
IT **Antibodies**
RL: BIOL (Biological study)
(to **blood-coagulation factor VIII**, chromatog. isolation and purification of, staphylococcal **protein** A in)
IT **Proteins**
RL: BIOL (Biological study)
(A, of Staphylococcus, in **blood-coagulation factor VIII antibody** isolation and purification)
IT 9001-24-5 **9001-27-8**
RL: BIOL (Biological study)
(**antibodies** to, chromatog. isolation and purification of, staphylococcal **protein** A in)

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